Attorney Docket No. 9233.0DV2

In re: Ekwuribe et al.

Appl. Serial No.: 09/430,735

Filed: October 29, 1999 Page 3 of 22

In the specification:

Please amend the specification as follows:

Please replace the section "BRIEF DESCRIPTION OF THE FIGURES," which begins on page 17, with the section as presented below:

3. BRIEF DESCRIPTION OF THE FIGURES

FIGURES 1A-1C: Formulae 8-10; amphiphilic oligomers of the present invention where in the lipophile is a sugar. In 1b and 1c, PEG is used as a spacer group. In 1A-1C a proline residue is added at the N-terminus of the enkephalin peptide. Hydrolysis cleaves the lipophilic moieties and generates a hydrophilic sugar-drug conjugate. Brain peptidases cleave the sugar moiety to generate a free peptide.

FIGURE 2: Compares the stability of the cetyl-PEG₂-enkephalin-lys (**SEQ ID NO:1**) conjugate (non- hydrolyzable) to unconjugated enkephalin (**SEQ ID NO:48**) in rat brain homogenate. (2% Rate Brain in PBS buffer, pH 7.4, 37 °C; Peptide = 60 µg/mL).

FIGURE 3: Compares the stability of the cetyl-PEG₃-enkephalin (**SEQ ID NO:1**) conjugate (non-hydrolyzable) to unconjugated enkephalin (**SEQ ID NO:47**) in rat brain homogenate. (2% w/v Rat brain in PBS buffer, pH 7.4, 37 °C; Peptide = $60 \mu g/mL$).

FIGURE 4: Compares palmitate-PEG₃-Enk (**SEQ ID NO:1**) conjugate (hydrolyzable) to unconjugated enkephalin (**SEQ ID NO:47**) in rat brain homogenate. (2% w/v Rat Brain in PBS buffer, pH 7.4, 37 °C; Peptide = 60 μg/mL).

FIGURE 5a-5d: HPLC data showing extraction of conjugate from homogenized rat brain.

HPLC conditions: Column: C-18; Solvent: solvent A = IPA; solvent B = Water +0.1% TFA;

Gradient: linear.

FIGURE 6: Graph demonstrating competitive binding between cetyl-PEG₂-enkephalin (**SEQ ID NO:1**) conjugate and naloxone, an Opioid μ receptor agonist.

Attorney Docket No. 9233.0DV2

In re: Ekwuribe et al.

Appl. Serial No.: 09/430,735

Filed: October 29, 1999

Page 4 of 22

FIGURE 7: Graphic comparison of analgesic effect of cetyl-PEG₂-enkephalin (SEQ ID NO:1) with clonidine (a morphine substitute).

FIGURE 8: Table showing results of receptor binding assays for various conjugates according to the present invention. Data are based on percent inhibition at a concentration of 100nM. The radioligand was DAMGO ([D-Ala2,N-Me-Phe-Gly5-ol]enkephalin) and naloxone served as the reference.

FIGURE 9: Exemplary synthetic scheme for an oligomer according to the present invention.

FIGURE 10: Exemplary synthetic scheme showing attachment of an oligomer to an enkephalin peptide according to the present invention.

Em H